REMARKS

THE SPECIFICATION

A number of minor typographical errors were noted upon review of the specification. Applicants submit replacement paragraphs in which such errors have been corrected.

No new matter has been added.

SPECIES ELECTION

Claim 1-38 were previously subject to a restriction requirement. Examiner also requested an election of species. As a result of Applicants' elections, Claims 6, 8-15, 21-25, 28, and 32-35 were withdrawn from consideration.

Claims 21-25, 28, and 32-35 are directed to a non-elected invention, and are now canceled.

However, Claims 6 and 8-15 are directed to a non-elected species, and therefore remain in this case. Applicants submit that §803.02 of the MPEP provides that the Examiner may require a provisional election of a single species prior to examination on the merits. This provisional election will be given effect *in the event* that the genus claim should be found not allowable. However, should no prior art be found that anticipates or renders obvious the elected species, the search of the genus claim should be extended.

REJECTION UNDER 35 U.S.C. §102(e) OR 35 U.S.C. §103(a)

Claims 1-5, 7, 16-20, 26-27, 29-31, and 36-38 have been rejected under 35 U.S.C. §102(e) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious over either U.S. Patent No. 6,245,227 to Moon et al. (hereinafter "Moon"), Moon or U.S. Patent No. 6,033, 546 to Ramsey (hereinafter "Ramsey I").

The claims as noted above are considered to read on either Moon or Ramsey I. The Office Action goes on to say that if a difference exists between the claims and either Moon or Ramsey I, it would reside in optimizing the elements of either Moon or Ramsey I. The Office Action then states that it would have been obvious to optimize the elements of either Moon or Ramsey I to enhance separation.

Anticipation of a claimed invention by a prior art reference under 35 U.S.C. §102 requires the presence in a single prior art reference of each and every element of a claimed

invention. Applicants respectfully submit that the Moon fails to disclose each and every element of the presently claimed devices.

To establish a *prima facie* case of obviousness under 35 USC 103(a), the Examiner must present a prior art reference which, when modified, teaches or suggests all the claim limitations. There must be some suggestion or motivation, either in the reference itself or in the reference providing the suggested modification, to modify the reference in order to teach or suggest all the claim limitations. In addition, there must be a reasonable likelihood of success, viewed in the light of the prior art. Here the Examiner is relying upon the Moon reference, in combination with Ramsey I. Based upon the foregoing requirements, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness.

Independent Claims 1, 26, 27, 29, and 36, all require that the microfluidic device have a gradient-generation means for generating a gradient of a selected mobile-phase component in a mobile phase or a mobile-phase source that provides a mobile phase that exhibits a gradient of a selected mobile-phase. Further, the gradient is generated by the use of pressure driven flow. This feature of the invention is not taught or suggested by Moon, for the reasons detailed below.

The Examiner needs look no further then applicant's specification to understand the difference between applicant's invention and that of Moon. From the description of the Figures, consider applicant's discussion of FIG. 1A on page 14, lines 3-16, which describes multiple inlet ports 48 and 50 and a mobile phase conduit 21, wherein each port can introduce a different mobile-phase component, i.e., each mobile-phase has a different concentration of a selected mobile-phase component. Diffusion of mobile- phase along the length of the holding conduit 21 provides a smooth gradient of the selected mobile-phase component. Similar discussions of a gradient-generation means for generating a gradient of a selected mobile-phase component in a mobile phase can be found on pages 15-16, lines 17-30, 1-4 (FIG. 2A), page 18, lines 20-26 (FIG.3) and page 26, lines 9-14 (FIG. 4).

Further, there is nothing in Moon comparable to applicant's considerations of the elements necessary "to ensure the proper formation of a smooth gradient" set forth in applicant's disclosure from line 5 of page 19 to line13 of page 22. In particular, note the design considerations for a gradient generation means as set forth in the paragraph on page 19, lines 5-18, namely residence time of the fluids in the mixing conduits, the differential flow resistance between the mixing conduits and the distribution and holding conduits, the

length of the cascade, plus additional design considerations to account for differences in viscosity between two separate mobile phases.

Examiner takes the position that a gradient generation means is disclosed in the Moon reference by citing col. 31, lines 27-35, of Moon as describing two additional reservoirs that produce gradient elution. Applicants argue that these few lines of Moon fail to adequately describe gradient generating means. The focus in Moon is a miniature electrospray device or system for electrospraying fluids (see claims 1 and 26 of Moon). Moon mentions that additional reservoirs downstream of the waste reservoir and upstream of the separation posts ***contain gradient elution of analytes in one reservoir*** and a diluent in the other reservoir. Col. 31, lines 27-35 of Moon does little more than suggest the **use** of gradient elution. Moon fails to provide an adequate description of a system providing gradient generating means or a method using gradient mobile-phase component generating means. The recitation in Moon relied on by Examiner cannot be construed to present a gradient generating means. For example, consider this sentence from Moon.

> "Additional reservoirs 410R, 410S downstream of the waste reservoir 410Q and upstream of the separation posts 416M ***may be provided to contain*** (emphasis added) gradient elution of analytes in one reservoir and a diluent in the other reservoir."(col.31, lines 27-30).

However it is neither clear how the gradient elution of Moon got into the reservoir nor how it was produced. The reference to "voltage differences" suggests electrokinetic pumping, but the Examiner's reference does not show any "gradient generating means," and provides an inadequate disclosure of electrokinetic pumping. This is not the same as or suggestive of creating a gradient using pressure driven flow, such as the "gradient generating means" produced by "pressure driven flow" of applicants' invention. Applicants have not claimed a gradient elution, but rather a means of generating one. .

Col. 30, line 64 to col. 31, line 2 (Fig. 35) of Moon describes the use of an upstream channel and posts for solid-phase extraction, as well as a waste reservoir. However, the ***use*** of a gradient elution is clearly not the same as a detailed description of a gradient generating means as provided in Applicant's disclosure and recited in applicant's claims. Examiner is mistaken that Moon teaches and/or suggests a gradient-generation means as is recited in the pending claims.

Although Moon is cited for ***a reservoir, containing a gradient elution of analytes***, such recitation is not the same as or even suggestive of applicant's recitation of ***an integrated gradient-generation means for generating a gradient of a selected mobile-phase component in a mobile phase*** as set forth in independent Claim 1. Applicants' "gradient generating means" is neither anticipated nor made obvious by Moon, whether such reference is considered singly or in combination with other references cited by Examiner

The Moon reservoir, containing a gradient elution of analytes, is not the same as or suggestive of the gradient-generation means recited in independent Claim 26. In particular, Claim 26 recites that the gradient-generation means comprises (i) a substrate having a microchannel with an upstream terminus and a downstream terminus, (ii) a cover plate arranged over the substrate surface, which in combination with the microchannel forms a mobile-phase holding conduit having a length defined by the upstream terminus and the downstream terminus, (iii) a plurality of inlet ports arranged along the length of the mobile-phase holding conduit, and (iv) an outlet port located downstream from the inlet ports of the mobile-phase holding conduit. Clearly, the plurality of inlet ports arranged along the length of the mobile-phase holding conduit, and the provision of an outlet port located downstream from the inlet ports of the mobile-phase holding conduit are elements of a gradient-generation means. Such gradient-generation means is neither taught nor suggested by Moon. More specifically, the Moon discussion at col. 31, lines 27-35, referred to by the Examiner neither teaches nor suggests the gradient-generation means of applicant's claim 26. Merely the ***use*** of a gradient elution is taught by that discussion.

The Moon reservoir, containing a gradient elution of analytes, is not the same as or suggestive of the integrated mobile-phase source recited in independent Claim 27. In particular, Claim 27 recites that the integrated mobile-phase source comprises a microconduit having a length defined by an upstream terminus and a downstream terminus, where the microconduit contains a mobile phase that exhibits a gradient of a selected mobile-phase component along the length of the microconduit. An integrated mobile-phase source having these elements is not taught or suggested by Moon. More specifically, this integrated mobile-phase source is not taught or suggested by the Moon discussion at col. 31, lines 27-35, referred to by the Examiner.

The Moon reservoir, containing a gradient elution of analytes, is not the same as or suggestive of the mobile-phase source recited in independent Claim 29. In particular, Claim 29 recites that the mobile-phase source comprises (i) a mobile-phase holding microconduit

having a length defined by an upstream terminus and a downstream terminus, and an outlet port located at the downstream terminus, and (ii) a mobile phase, contained in the mobile-phase holding microconduit, that exhibits differing concentrations of selected mobile-phase component along the length of the mobile-phase holding microconduit. A mobile-phase source having these elements is not taught or suggested by Moon. More specifically, this mobile-phase source is not taught or suggested by the Moon discussion at col. 31, lines 27-35, referred to by the Examiner.

The Moon reservoir, containing a gradient elution of analytes, is not the same as or suggestive of the microfluidic device recited in independent Claim 36. In particular, Claim 36 recites that the microfluidic device comprises a means for producing different concentrations of a selected mobile-phase component in different locations within a mobile phase, a plurality of mobile-phase sources each containing a mobile phase, and a means for introducing plugs of mobile phase from the mobile-phase sources through the at least one inlet port into the mobile-phase holding conduit such that the plugs are arranged in a predetermined order along the length of the mobile-phase holding conduit. A microfluidic device having these elements is not taught or suggested by Moon. More specifically, these elements of the microfluidic device are not taught or suggested by the Moon discussion at col. 31, lines 27-35, referred to by the Examiner.

Ramsey I describes a continuous flow device wherein the outputs of multiple reservoirs converge at a common intersection, a structure which is quite unlike the gradient generation means of applicant's invention. For example, Ramsey I lacks structure comparable to the mixing conduits of applicant's invention.

Applicants submit that neither the cited Moon reference nor the cited Ramsey I reference teach the invention as presently claimed. Applicants further submit that the cited Moon reference, whether viewed alone or in combination with the cited Ramsey I reference, fails to suggest the invention as presently claimed. Accordingly, Applicants submit that the invention is patentable under 35 U.S.C. §102(e) and 35 U.S.C. §103(a) when considered against such references and respectfully request reconsideration and withdrawal of these rejections.

Claims 1-5, 7, 16-20, 26-27, 29-31, and 36-38 are also rejected under 35 U.S.C. §103(a) as being unpatentable over Moon, or in the alternative under 35 U.S.C. §103(a) as being obvious over either Moon or Ramsey I in view of. U.S. Patent No. 6,110,643 to

Ramsey et al (hereinafter "Ramsey II") and U.S. Patent No. 6,012,902 to Parce et al. (hereinafter "Parce").

The claims as noted above are considered by Examiner to differ "at best" from either Moon or Ramsey I in reciting use of pressure driven flow. The Office Action goes on to say that Ramsey II discloses that a hydraulic force is an alternative to use of an electrically driven force in delivering fluids through the channels of a micro chip (column1, lines 10-18). The Office Action then cites Parce (column 3, lines 6-32) for the proposition that use of a micropump to generate a flow is useful where pressure based flow is particularly desirable, where electric fields are prohibited, and where materials are not easily or predictably transported by electrokinetic flow. Finally the Examiner states that it would have been obvious to use pressure driven flow in either Moon or Ramsey I because Ramsey II discloses that a hydraulic force is an alternative to use of an electrically driven force in delivering fluids through the channels of a micro chip and because Parce discloses that use of a micropump to generate a flow is useful where pressure based flow is particularly desirable, where electric fields are prohibited, and where materials are not easily or predictably transported by electrokinetic flow.

Because Ramsey II is provided by the Examiner for the proposition that a hydraulic force is an alternative to use of an electrically driven force in delivering fluids through the channels of a micro chip and Parce is provided by the Examiner for the proposition that use of a micropump to generate a flow is useful where pressure based flow is particularly desirable, and neither of these references discloses a gradient generation means like that claimed by applicants, Applicants submit that the invention is patentable under 35 U.S.C. §103(a) when considered against such references whether singly or in combination with the Moon and Ramsey I references and respectfully request reconsideration and withdrawal of the 35 U.S.C. §103(a) rejection as stated above.

SUMMARY

The above arguments are submitted for the purpose of facilitating allowance of the Claims and a sincere effort has been made to place this application in condition for allowance. An early notice of allowance is earnestly requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 330-0900.

Respectfully submitted,

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